

**IN THE DRAWINGS:**

The attached sheets of drawings include changes to Figures 1-2. These sheets, which include Figures 1-2, replace the previous drawing sheets, including Figures 1-2.

Attachments: Replacement Sheets (Exhibit C)

**REMARKS**

The amendments to the specification, claims and drawings are described below in italics, followed by an explanation of why the amendment does not contain new matter.

The following remarks pertain to the amendments of the specification:

*On page 1, line 15, endnote numbers "2a, 11a" are deleted and replaced with --1a, 10a--.* The description of the reference in the specification, together with the disclosure inherent in the published reference, is sufficient to identify references 1a and 10a as the correct reference.

*On page 2, line 24, "2-chloro-deoxyadenosine" is deleted and replaced with --2-chloro-2'-deoxyadenosine--.*

*On page 2, line 24, "2-amino-deoxyadenosine" is deleted and replaced with --2-amino-2'-deoxyadenosine--.*

*On page 2, line 25, "deazoniation" is deleted and replaced with --dediazonation--.*

The cited reference, U.S. Patent 6,596,858 expressly and inherently describes the correct chemical name, as well as the correct name (dediazonation) of the reaction.

*On page 3, the sentence spanning lines 1-3 is deleted and replaced with --This method, however, creates various impurities, which requires extensive purification procedures, and results in an overall yield of only 27%.--*

*On page 3, line 5, after "result in a more", --purified-- is added.*

This amendment merely clarifies and more correctly describes what is inherently disclosed in the prior art reference.

*On page 3, line 18, "deoxyguanosine" is deleted and replaced with --2'-deoxyguanosine--.* This amendment merely clarifies with more specificity the starting compound **1a**, which is described elsewhere in the specification on page 11, line 3, and in the Examples.

*On page 3, line 19, "diazonization" is deleted and replaced with --diazotization--.* This amendment corrects the name of the reaction, and is obvious because "diazotization" is the correct name of the reaction described, and one skilled in the art would recognize that the correct name of the reaction is "diazotization".

*On page 7, line 1, "obtained" is deleted and following the number "(85%)," the words --were obtained-- are added.* This amendment is made to correct a grammatical error.

*On page 7, line 14, "2.6-dichloropurine" is deleted and replaced with --2,6-dichloropurine--.* This amendment replaces a period with a conventional comma.

*On page 7, line 21, following the word "nitrite", a right parenthesis --)-- is added.* This amendment adds a right parenthesis to match the preceding left parenthesis.

*On page 8, line 10, "diehloropurine" is deleted and replaced with --dichloropurine--.* This amendment corrects an obvious spelling error.

*On page 8, line 15, the endnote number "38" is deleted and replaced with --35--.* This amendment adds a correct reference number, which corresponds to the description of the method described.

*On page 9, line 14, "DMS" is deleted and replaced with --DMF--.* This amendment adds the correct term "DMF" which is the correct synonym for "tetrahydrofuran".

*On page 10, line 12, "methylalkoxides" is deleted and replaced with --metal alkoxides--.* This amendment adds the correct name of the compound, which is well known in the art as the

basic reagent used for deacylation of the R protecting groups. It is well known in the art that “methyl” alkoxide is not a deacylation reagent.

*On page 12, line 6, the regular font “1a” is deleted and replaced with bold font --1a--.*

*On page 12, line 17, the regular font “1b” is deleted and replaced with bold font --1b--.*

*On page 12, line 18, the regular font “2b” is deleted and replaced with bold font --2b--.*

*On page 13, line 19, the regular font “2a” is deleted and replaced with bold font --2a--.*

*On page 13, line 21, the regular font “2a” is deleted and replaced with bold font --2a--.*

*On page 13, line 25, the regular font “3a” is deleted and replaced with bold font --3a--.*

*On page 14, line 9, the regular font “2b” is deleted and replaced with bold font --2b--.*

*On page 14, line 10, the regular font “3b” is deleted and replaced with bold font --3b--.*

*On page 14, line 17, the regular font “2’b” is deleted and replaced with bold font --2’b--.*

*On page 14, line 18, the regular font “3’b” is deleted and replaced with bold font --3’b--.*

All of the above amendments change the font to bold, to be consistent with the bold numbering described in the drawings and examples.

*On page 15, line 8, the reference to endnote “39” is deleted and replaced with--38--.*

This amendment is made because there were two identical endnotes, 38 and 39, and the duplicate endnote 39 was deleted, requiring the above amendment. It is obvious because it still references the same publication.

*On page 15, line 25, the reference to endnote “40” is deleted and replaced with --39--.*

This amendment was made because the deletion of endnote 39 shifted the numbering of endnote 40 to endnote 39. It is obvious because it still references the same publication.

*On page 18, line 6, "hexames" is deleted and replaced with --hexanes--.* This amendment deletes the term "hexames," which is an obvious typographical error, and replaces it with "hexanes," a known term.

*On page 21, endnote 27, "Shibya" is deleted and replaced with --Shibuya--, and a space is added following --M.J. --.* This amendment corrects the name of the publication's author.

*On page 21, endnote 39 is deleted.* This amendment removes a duplicate of endnote 38.

*On page 21, endnote 40, the number "40" is deleted and replaced with --39--.* This amendment puts the endnotes in sequential order.

*On page 28, in the abstract, last line, following "selectively replaced" the words --with a 6-amino-- were added.* This amendment corrects a grammatical error.

The following remarks pertain to amendments of the claims (only the portion amended is reproduced in italics):

Claim 1 is amended as follows: *...(b) replacing the 2-amino group with a 2-chloro group by a diazotization/chloro-dediazoniation reaction...* This amendment merely corrects an obvious spelling error, the correct spelling of which is found, for example, in the specification, page 5, lines 5-7.

Claim 5 is amended as follows: *...(a) converting the 6-oxo group of a compound having the formula ... wherein R is a protecting group selected from the group consisting of acetyl, benzoyl, into a 6-leaving group having greater reactivity than that of the ~~2-chloro~~ 2-amino group in a diazotization/chloro-dediazoniation ~~an S<sub>N</sub>A<sub>2</sub>~~ displacement reaction...* This amendment merely corrects an obvious error, so as to be consistent with the specification. Basis for the amendment is found in the specification, page 5, lines 5-7.

Claim 6 is amended as follows: ...*(c) reacting the product of step (b) with ammonia in a compatible solvent ~~or with a~~ compatible with nitrogen source capable of being converted to an amino group in a solvent compatible with the nitrogen source to replace the 6-leaving group with a 6-amino group by selective ammonolysis of the 6-leaving group...* This amendment is made to make the language of the claim consistent with the language of the specification, for example, on page 9, lines 1-15.

The following remarks pertain to the amendments of the drawings:

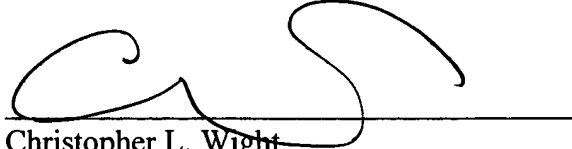
*Figure 1, compound 4, is amended by replacing the -OR groups at the 3 and 5 position on the pentofuranosyl ring with -OH groups.* Support for this amendment can be found in Example 11 on page 16, which identifies compound 4 as 2-Chloro-2'-deoxyadenosine, which by definition has -OH groups at the 3 and 5 position on the pentofuranosyl ring.

*Figure 1, compound 4, is also amended by deleting the hydrogen at the 1 position on the purine ring.* This error is obvious in view of the fact that the reaction from compound 3 to 4, and 6 to 4, would result in -N-, not -NH-, and further in view of the fact that the end product, compound 4, is identified as cladribine, a known product having -N- at the 1 position.

*The caption of Figure 2 is amended by replacing the reference "NO2" with --NO<sub>2</sub>--.*

This merely corrects an obvious formatting error.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'CW', is written over a horizontal line.

Christopher L. Wight  
Reg. No. 31,680  
Holland & Hart LLP  
555 17th Street, Suite 3200  
Denver, Colorado 80201-8749  
Telephone: (801) 595-7823  
Fax: (801) 364-9124

Date: March 25, 2005  
CLW/jml

10/529106

JC17 Rec'd PCT/PTO 25 MAR 2005

**UNITED STATES UTILITY PATENT APPLICATION**

**OF**

**Morris J. Robins, Zlatko Janeba, and Paula Francom**

**FOR**

**Method for the Preparation of 2-Halo-2'-Deoxyadenosine**

**Compounds from 2'-Deoxyguanosine**



**TITLE OF THE INVENTION**

Method for the Preparation of 2-Halo-2'-Deoxyadenosine Compounds from 2'-Deoxyguanosine.

**CROSS-REFERENCE TO RELATED APPLICATIONS**

5        This application is a 371 national phase of PCT/US2003/030386, filed September 25, 2003, and claims the benefit of US Provisional Application No. 60/413,915, filed September 25, 2003, and US Provisional Application No. 60/416,329, filed October 4, 2002.

**FIELD OF THE INVENTION**

10        The present invention is directed to processes for preparing 2-halo-6-aminopurines, and more particularly to a process for preparing 2-chloro-2'-deoxyadenosine.

**BACKGROUND OF THE INVENTION**

15        The lymphoselective toxicity of 2-chloro-2'-deoxyadenosine (CldAdo, cladribine) and its potential as a chemotherapeutic agent against lymphoid neoplasms were reported by Carson et al.<sup>1</sup> This potent, deaminase-resistant analogue of 2'-deoxyadenosine (dAdo) is currently the drug of choice for hairy-cell leukemia.<sup>2,3</sup> It also has significant activity against chronic lymphocytic leukemia,<sup>4,5</sup> indolent non-Hodgkin's lymphoma,<sup>6</sup> and Waldenström's macroglobulinemia.<sup>7</sup> Investigations with cladribine treatment of multiple sclerosis,<sup>8</sup> systemic lupus erythematosus-associated glomerulonephritis,<sup>9</sup> and other rheumatoid and immune disorders are in progress. Cladribine is a nucleoside prodrug, which is phosphorylated by deoxycytidine kinase to CldAMP, and then sequentially to CldADP and the active CldATP.<sup>21, 11a-1a, 10a</sup> Cladribine also is a good substrate for mitochondrial 2'-deoxyguanosine (dGuo) kinase,<sup>10</sup> and induction of programmed cell death by direct effects on mitochondria has been implicated in its potent activity against indolent lymphoid malignancies (via apoptosis) as well as in proliferating cells.<sup>11,12</sup>

20

Various methodologies have been published for the production of Cladribine. Venner reported Fischer-Helferich syntheses of naturally occurring 2'-deoxynucleosides in 1960,<sup>13</sup> and employed 2-chloro-2'-deoxyadenosine as an intermediate for 2'-deoxy(guanosine and inosine). Ikehara and Tada also synthesized dAdo with CldAdo as an intermediate [obtained  
5 by desulfurization of 8,2'-anhydro-9-( $\beta$ -D-arabinofuranosyl)-2-chloro-8-thioadenine].<sup>14</sup>

Syntheses of CldAdo as a target compound have exploited the greater reactivity of leaving groups at C6 relative to those at C2 of the purine ring in  $S_NAr$  displacement reactions. Robins and Robins<sup>15</sup> employed fusion coupling of 2,6-dichloropurine with 1,3,5-tri-*O*-acetyl-2-deoxy- $\alpha$ -D-ribofuranose. The 9-(3,5-di-*O*-acetyl-2-deoxy- $\alpha$ -D-*erythro*-pentofuranosyl)-  
10 2,6-dichloropurine anomer was obtained by fractional crystallization. Selective ammonolysis at C6 and accompanying deprotection gave 6-amino-2-chloro-9-(2-deoxy- $\alpha$ -D-*erythro*-pentofuranosyl)purine. The pharmacologically active  $\beta$ -anomer (cladribine) was prepared by an analogous coupling, chromatographic separation of anomers, and ammonolysis.<sup>16</sup>

Stereoselective glycosylation of sodium salts of halopurines and analogues with 2-  
15 deoxy-3,5-di-*O*-*p*-toluoyl- $\alpha$ -D-*erythro*-pentofuranosyl chloride gave  $\beta$ -nucleoside anomers via predominant Walden inversion,<sup>17,18</sup> and ammonolysis/deprotection gave CldAdo.<sup>19</sup> Although the sodium salt glycosylation usually gave good anomeric stereoselectivity, minor quantities of  $\alpha$  anomers and >10% of N7 regioisomers were usually formed.<sup>20,21</sup> This requires separations and results in diminished yields of the desired N9 product. Carson et al.<sup>1</sup>  
20 had reported an enzymatic transfer of the 2-deoxy sugar from thymidine to 2-chloroadenine (ClAde). Holy and coworkers noted that cells of a strain of *Escherichia coli* performed glycosyl transfer from 2'-deoxyuridine to 2-chloro-6-  
[(dimethylaminomethylene)amino]purine to give a derivative of CldAdo.<sup>22</sup> Very recently Barai, Mikhailopulo, and coworkers<sup>23</sup> described an *E. coli*-mediated glycosyl transfer  
25 synthesis of 2,6-diamino-9-(3-deoxy- $\beta$ -D-*erythro*-pentofuranosyl)purine,<sup>24</sup> and its enzymatic

deamination to 3'-deoxyguanosine.<sup>24</sup> They reported glycosyl transfer from 2'-deoxyguanosine to ClAdo, and claimed a yield of 81% of ClAdo (based on ClAdo).<sup>23</sup> However, a 3:1 ratio of dGuo/ClAdo was employed, so the yield of ClAdo was <27% based on dGuo.

5        Sampath et al. have recently shown (U.S. Patent No. 6,596,858 B2) a method for making ~~2-chloro-deoxyadenosine~~ 2-chloro-2'-deoxyadenosine compounds, using 2-amino-2'-deoxyadenosine ~~2-amino-2'-deoxyadenosine~~ as a starting compound, but beginning with an initial diazotization/chloro-~~deazoniatio~~nediazoniation reaction on the unprotected nucleoside to replace the 2-amino group with a 6-chloro group. ~~Subsequent steps, however,~~  
 10 ~~create various stereo- and region-isomeric impurities, resulting in an overall yield of only 27%. This method, however, creates various impurities, which requires extensive purification procedures, and results in an overall yield of only 27%.~~

Accordingly, there is a significant need to produce ClAdo using methods that result in a higher yield, are more cost effective, and result in a more purified form.

## 15        SUMMARY OF THE INVENTION

The present invention is a method for producing 2-chloro-2'-deoxyadenosine (ClAdo) comprising the steps of: (a) converting the 6-oxo group of a compound having the formula (1) wherein R is a protecting group, into a 6-leaving group having sufficient reactivity for an S<sub>N</sub>Ar displacement reaction; (b) replacing the 2-amino group with a 2-chloro  
 20 group in a diazotization/chloro-dediazoniatio reaction; (c) replacing the 6-leaving group with a 6-amino group; and (d) removing the R protecting groups, to produce 2-chloro-2'-deoxyadenosine.

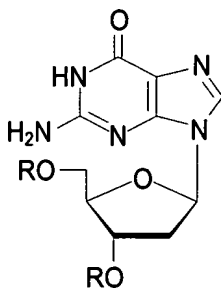
## DESCRIPTION OF THE FIGURES

Figure 1 shows the chemical synthesis of 2-chloro-2'-deoxyadenosine from protected  
 25 forms of naturally occurring ~~deoxyguanosine~~ 2'-deoxyguanosine.

Figure 2 shows the ~~diazonization~~diazotization/halo-dediazoni-  
 ation conversion reaction from a 2-aminopurine nucleoside to a 2-halopurine nucleoside.

### **DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION**

In accordance with the present invention, synthesis of regio- and stereochemically  
 5 pure 2-chloro-2'-deoxyadenosine (Cladrabine, or CldAdo), which avoids separation of  
 mixtures with fusion and sodium salt glycosylation procedures, is accomplished by  
 transformation of the naturally occurring nucleoside 2'-deoxyguanosine (dGuo) as the  
 starting compound.<sup>24</sup> Methods for producing CldAdo from 2'-deoxyguanosine (dGuo)  
 according to the present invention begin with protected forms of dGuo including, but not  
 10 restricted to, acyl, silyl, amide, and other derivatives useful in the field of  
 nucleoside/nucleotide/nucleic acid chemistry and protection strategies. Methods for  
 obtaining protected forms of dGuo are well-known in the art.<sup>25,26,27,28,29,30</sup> The preferred  
 starting products for efficient synthesis of CldAdo are defined by the following chemical  
 structure:



where R is any suitable protecting group, and preferably R is Ac or Bz.

In order to obtain the desired CldAdo compounds, protected dGuo derivatives are  
 20 treated with combinations of chemicals that effect functionalization at the C6 position to give  
 groups that can be replaced, followed by transformation of the 2-amino function to a 2-chloro

group, followed by replacement of the 6-functional group to give a 6-amino group (or a 6-substituent that can be converted into a 6-amino group, followed by conversion to the 6-amino group), and concomitant or subsequent deprotection of the resulting 6-amino-2-chloropurine derivative to give CldAdo. For example, from dGuo, CldAdo (**4**) (Figure 1) is synthesized by converting the 6-oxo function into appropriate 6-(substituted oxy) leaving groups that can be replaced without protection of the 2-amino moiety, transformation of the 2-amino function to a 2-chloro functional group by diazotization/chloro-dediazotiation of the 2-amino function, and selective C6 ammonolysis of the 2-chloro-6-(substituted)purine derivatives, with accompanying sugar deprotection. This route advantageously provides retention of both  $\beta$ -anomeric stereochemistry and N9 isomeric purity.

Functionalization of the 6-oxo group is accomplished by converting, without protection of the 2-amino moiety, the 6-oxo group to a 6-(substituted oxy) leaving group having greater reactivity than the 2-chloro group in a  $S_NAr$  displacement reaction. Two preferred methods for functionalization at the C6-oxy group include alkyl- or arylsulfonylation of the C6-oxy group and chlorodeoxygenation at C6.

Alkyl- or arylsulfonylation of the C6-oxy group can be accomplished by treating protected dGuo derivatives with (alkyl or any substituted alkyl or cycloalkyl)sulfonyl, phosphoryl or phosphonyl reagents or (aryl or any substituted aryl)sulfonyl, phosphoryl or phosphonyl reagents, which include, for example, sulfonyl compounds having the formula  $R'SO_2-X$ , where X is a halogen (such as chloride), imidazolide, triazolide or tetrazolide and R' is alkyl, substituted alkyl (including but not limited to fluoroalkyl), cycloalkyl, aryl, or substituted aryl, to convert the 6-oxo group to a 6-O-(alkyl, substituted alkyl, cycloalkyl, aryl or substituted aryl)sulfonyl group. In preferred embodiments, 3',5'-di-O-(acetyl or benzoyl)-2'-deoxyguanosine (**1**) is treated with (2,4,6-triisopropyl or 4-methyl)benzenesulfonyl chloride, to give high yields of the 6-O-arylsulfonyl derivatives **2** or **2'b**. In other preferred

embodiments, **1** is treated with TiPBS-Cl, which gives the 6-*O*-TiPBS derivative **2a** or **2b**, or TsCl, which gives the 6-*O*-Ts derivative **2'b**.

Several acyl-protected 6-*O*-sulfonyl derivatives of dGuo that can be utilized are known in the art.<sup>28,29,30</sup> Treatment of 3',5'-di-*O*-acetyl-2'-deoxyguanosine<sup>31</sup> (**1a**) or its 3',5'-di-*O*-benzoyl analogue **1b**<sup>31</sup> with TiPBS-Cl/Et<sub>3</sub>N/DMAP/CHCl<sub>3</sub> by the general method of Hata et al.<sup>29</sup> gave the 6-*O*-TiPBS derivatives **2a**<sup>32</sup> (91%) or **2b** (86%), respectively. Similar treatment of **1b** with TsCl/Et<sub>3</sub>N/DMAP/CHCl<sub>3</sub> gave the 6-*O*-Ts derivative **2'b** (89%).

Efficient displacement of sulfonate from C6 in following steps requires a sterically hindered arylsulfonyl derivative. A more economical 6-*O*-tosyl derivative gave lower yields at the final stage owing to attack of ammonia at both sulfonyl sulfur and C6 (**3'b** gave **4** in 43% yield). By contrast, ammonolysis of the 6-*O*-TiPBS derivatives proceeded efficiently at C6 with minimal attack at the hindered sulfur atom. Both types of such arylsulfonate derivatives, and especially the 6-*O*-Ts, underwent increased nucleophilic attack at sulfur with lower temperatures (−20 to 0 °C) to give 6-oxopurine derivatives, resulting in a lower yield.

However, treatment of the 6-*O*-TiPBS compounds with NH<sub>3</sub>/MeOH/CH<sub>2</sub>Cl<sub>2</sub> in a pressure tube at 80 °C strongly favored nucleophilic attack at C6 to give good yields of CldAdo (**4**).

Alternatively, the 6-oxo group can be replaced by a 6-chloro leaving group by chlorodeoxygenation at C6. Chlorine is the most frequently used leaving group at C6 of purine nucleosides. Methods for producing CldAdo from dGuo begin with protected forms of dGuo described above and involve treatment of such derivatives with combinations of chemicals that convert the 6-oxo function into a 6-chloro group that can be replaced on the resulting 2-amino-6-chloropurine derivative. Deoxychlorination at C6 of **1** results in excellent yields of the 2-amino-6-chloropurine derivatives **5**. In preferred embodiments, protected dGuo derivatives are treated with phosphoryl chloride, a source of soluble chloride,

an organic base, and acetonitrile or other compatible solvent, to convert the 6-oxo function into a 6-chloro group.

Original studies on deoxychlorination of guanosine<sup>33</sup> (Guo) and dGuo<sup>34</sup> derivatives with POCl<sub>3</sub> gave moderate (Guo) to poor (dGuo) yields of 2-amino-6-chloropurine products, and improved procedures have been reported.<sup>26a,35,36</sup> The acid-labile 2'-deoxy derivatives 1 were deoxychlorinated with POCl<sub>3</sub>/*N,N*-dimethylaniline/BTEA-Cl/MeCN/ $\Delta$ ,<sup>26a,36</sup> and ~~obtained~~ 6-chloro derivatives **5a** (90%) and **5b** (85%) were obtained in high yields under carefully controlled conditions.

Following the step of converting the 6-oxo group to a 6-(substituted oxy) leaving group, the 2-amino group is replaced with a 2-chloro group by a diazotization/halo-dediazoni-  
ation reaction. Improved methods are disclosed for replacement of an amino group on purine nucleoside derivatives with chlorine, bromine, or iodine under non-aqueous conditions by diazotization/halo-dediazoni-  
ation methods.<sup>27</sup> These mild diazotization/halo-dediazoni-  
ation methods are applicable at C6 of dAdo derivatives as well as at C2 of 2-amino-6-chloropurine nucleosides. In accordance with the present invention, CldAdo is produced from dGuo by treatment of protected forms of dGuo that contain a respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl group with reagents that effect diazotization/chloro-dediazoni-  
ation at C2 to give a 2-chloro group. CldAdo is also produced by treating protected 2-amino-6-chloropurine derivatives with reagents that effect diazotization/chloro-dediazoni-  
ation at C2 to give respective ~~2,6-dichloropurine~~ 2,6-dichloropurine derivatives.

Reagents that effect diazotization/chloro-dediazoni-  
ation at C2 to give a 2-chloro group include a halide source (such as metal chlorides, metal chloride salts, acyl chlorides, sulfonyl chlorides, and silyl chlorides, alkyl and aryl substituted ammonium chloride salts, including but not limited to tetraalkyl and aryl ammonium chloride salts) and a nitrite source (such as metal nitrites, metal nitrite salts, organic nitrites, such as tert-butyl nitrite, pentyl

nitrite, and isoamyl nitrite, and complex quaternary ammonium nitrites, such as benzyltriethylammonium ~~nitrite~~ nitrite).

In preferred embodiments of the present invention, CldAdo is synthesized by employing acetyl chloride and benzyltriethylammonium nitrite (BTEA-NO<sub>2</sub>)-mediated  
 5 diazotization/chloro-dediazoni-ation of 6-*O*-(2,4,6-triisopropylbenzenesulfonyl) (TiPBS) or 6-chloro derivatives that are readily obtained from dGuo. Non-aqueous diazotization/chloro-dediazoni-ation (acetyl chloride/benzyltriethylammonium nitrite) of **2**, **2'b**, or **5** gave the 2-chloropurine derivatives **3**, **3'b**, or **6**, respectively. This new procedure for non-aqueous diazotization/chloro-dediazoni-ation<sup>27</sup> (AcCl/BTEA-NO<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>/–5 to 0 °C) worked well for  
 10 replacement of the 2-amino group of **2**, **2'b**, and **5** with chlorine to give **3a** (89%), **3b** (90%), **3'b** (87%), **6a** (95%), and **6b** (91%).

Efficient diazotization/chloro-dediazoni-ation of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine<sup>26,33</sup> (**7**) (Figure 2) was effected with TMS-Cl (9 equivalents) and benzyltriethylammonium nitrite (BETA-NO<sub>2</sub>) (3 equivalents) in CH<sub>2</sub>Cl<sub>2</sub> at  
 15 ambient temperature. The process was rapid (<30 min), and the desired 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-~~dichloropurine~~ dichloropurine<sup>27,37</sup> (**8**) (83%, without chromatography) was obtained as a white crystalline solid. Comparable yields were obtained at 0° C. TMS-Cl (3.5 equivalents) and BTEA-NO<sub>2</sub> (1.5 equivalents) with powdered NaNO<sub>2</sub> (5 equivalents) gave **8** (86%) within 1 hr. By contrast, an alternative method for non-aqueous  
 20 diazotization/chloro-dediazoni-ation of **7** employed Cl<sub>2</sub>/TBN/CuCl in a strongly exothermic reaction, and removal of colloidal material by filtration was required prior to crystallization of **7**.<sup>38-35</sup>

Compound **7** underwent efficient diazotization/bromo-dediazoni-ation with TMS-Br and tert-butyl nitrite (TBN). Competing redox interactions between nitrite anion and TMS-  
 25 Br precluded the use of NaNO<sub>2</sub>. The 2-bromo-6-chloropurine nucleoside **3**<sup>27,37</sup> (85%, without



chromatography) was obtained as a crystalline solid with TMS-Br (9 equivalents)/TBN (20 equivalents)/CH<sub>2</sub>Br<sub>2</sub>/ambient temperature within 1 h.

NOCl/CH<sub>2</sub>Cl<sub>2</sub> or NOBr/CH<sub>2</sub>Br<sub>2</sub> is presumed to be generated from (Me<sub>3</sub>SiX or AcCl) and (TBN or BTEA-NO<sub>2</sub>). These procedures provide efficient diazotization/halo-  
 5 dediazonation of protected (2 or 6)-aminopurine nucleosides as well as the acid-sensitive 2'-deoxynucleosides. The reactions are cost-effective and proceed at or below ambient temperature with convenient reagents and standard laboratory equipment and conditions.

Following replacement of the 2-amino group with a 2-chloro group, the protected forms of dGuo that contain a respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl or phosphoryl  
 10 group and a 2-chloro group is reacted with chemicals that cause replacement of the 6-*O*-(alkyl, cycloalkyl, or aryl) sulfonyl or phosphoryl group to give a 6-amino group (or a substituent that can be converted into a 6-amino group, resulting in overall conversion of the substituent into a 6-amino group) of a resulting 6-amino-2-chloropurine derivative. In preferred embodiments, the 6-leaving group is replaced with a 6-amino group by reacting the  
 15 product of step (b) with a nitrogen source capable of being converted to an amino group in a solvent compatible with the nitrogen source to replace the 6-leaving group with a 6-amino group by selective ammonolysis of the 6-leaving group. The nitrogen source is selected from the group consisting of ammonia, azides, hydrazines, benzylic amines, or compatible ammonium salts. The solvent may be any solvent that is compatible with the nitrogen source,  
 20 such as methanol, ethanol, higher alcohols, or aprotic solvents, such as 1,2-dimethoxyethane, tetrahydrofuran, or ~~DMS~~-DMF.

In other preferred embodiments, the respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl leaving group is reacted with ammonia in a compatible aprotic solvent to give a 6-amino-2-chloropurine derivative, followed by deprotection (if necessary) to give CldAdo. In a more  
 25 preferred embodiment, a 9-(3,5-di-*O*-acyl-β-D-*erythro*-pentofuranosyl-6-*O*-(alkyl,

cycloalkyl, or aryl)sulfonyl-2-chloropurine is treated with ammonia in methanol or other compatible solvent to give CldAdo.

Further, protected derivatives of 2,6-dichloropurine are treated with reagents that cause selective replacement of the 6-chloro group to give a 6-amino group (or a substituent  
 5 that can be converted into a 6-amino group, followed by conversion of the substituent into a 6-amino group) of a resulting 6-amino-2-chloropurine derivative. In a more preferred embodiment, 9-(3,5-di-*O*-acyl- $\beta$ -D-*erythro*-pentofuranosyl)-2,6-dichloropurine is treated with ammonia in methanol or other compatible solvent to give CldAdo.

Selective ammonolysis at C6 (arylsulfonate with **3** or chloride with **6**) and  
 10 accompanying deprotection of the sugar moiety gave CldAdo (**4**) (64–75% overall from **1**). Specifically, displacements of the hindered arylsulfonate (from **3**) or chloride (from **6**) at C6 with accompanying cleavage of the sugar esters were effected at 80 °C with NH<sub>3</sub>/MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Cladribine (**4**) was obtained in high yields from **3a** (81%), **3b** (83%), **6a** (87%), and **6b** (94%), but only in moderate yield from the 6-*O*-tosyl derivative **3'b** (43%).

15 The R protecting groups are removed by deacylation using a basic reagent well known in the art in a solvent compatible with the basic reagent, to remove the R protecting groups and produce 2-chloro-2'-deoxyadenosine. The basic reagent is selected from the group consisting of ammonia, ~~methylalkoxides~~ metal alkoxides, metal hydroxides, and metal carbonates. The solvent may be any solvent that is compatible with the basic reagent, such as  
 20 methanol, ethanol, 1,2-dimethoxyethane/H<sub>2</sub>O, or tetrahydrofuran/H<sub>2</sub>O.

It is to be noted that removal of the R protecting groups may occur concomitantly with or subsequent to the replacement of the 6-(substituted oxy) leaving group with a 6-amino group by ammonolysis. Both steps of replacement of the 6-(substituted oxy) leaving group with a 6-amino group and removal of the R protecting groups is accomplished by use  
 25 of a nitrogen source in a solvent compatible with the nitrogen source. Where the nitrogen

source is ammonia in a protic solvent, such as methanol or ethanol, both steps proceed simultaneously. However, where the nitrogen source is anhydrous ammonia in a dry solvent, such as 1,2-dimethoxyethane, or tetrahydrofuran, only the step of replacement of the 6-(substituted oxy) leaving group with a 6-amino group proceeds. In this case, it is necessary and sometimes desirable to remove the R protecting groups in a separate step.

In the most preferred embodiments of the present invention, synthesis of the clinical drug cladribine (2-chloro-2'-deoxyadenosine, CldAdo, **4**) was accomplished in three steps from the readily available 3',5'-di-*O*-acetyl-2'-deoxyguanosine (**1a**) or its dibenzoyl analogue **1b**. Replacement of the 2-amino group proceeded in high yields by diazotization/chlorodediazotiation with AcCl/BTEA-NO<sub>2</sub>. Selective ammonolysis of **3a** and **3b** (6-OTiPBS) or **6** (6-Cl), with accompanying deacylation, gave **4** (64–75% overall). Ammonolysis of **3'b** (6-OTs) was problematic and gave **4** in poor overall yield (33%). Routes that employed deoxychlorination of **1** were ~10% more efficient overall than those which involved 6-*O*-TiPBS intermediates.

## EXAMPLES

Melting points for **4** were determined with a hot-stage apparatus. UV spectra were recorded with solutions in MeOH. <sup>1</sup>H NMR spectra were recorded at 300 MHz with solutions in CDCl<sub>3</sub> unless otherwise indicated. "Apparent" peak shapes are in quotation marks when first-order splitting should be more complex or when peaks were poorly resolved. Mass spectra (MS) were determined with FAB (glycerol) unless otherwise indicated. Chemicals and solvents were of reagent quality. CH<sub>2</sub>Cl<sub>2</sub> and MeCN were dried by reflux over and distillation from CaH<sub>2</sub>. CHCl<sub>3</sub> was dried over P<sub>2</sub>O<sub>5</sub> and distilled. AcCl, POCl<sub>3</sub>, and *N,N*-dimethylaniline were freshly distilled before use. Benzyltriethylammonium nitrite (BTEA-NO<sub>2</sub>) was prepared from BTEA-Cl by ion exchange [Dowex 1 X 2 (NO<sub>2</sub><sup>-</sup>)].

Column chromatography (silica gel, 230–400 mesh) was performed with CH<sub>2</sub>Cl<sub>2</sub>/MeOH. Compounds **1a** and **1b** were prepared as described.<sup>31</sup>

Method 1 (nucleoside/TiPBS-Cl/DMAP/ Et<sub>3</sub>N/CHCl<sub>3</sub>) is described for **1a** → **2a**, method 2 (nucleoside/AcCl/BTEA-NO<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>) for **2a** → **3a**, method 3 (nucleoside/*N,N*-dimethylaniline/POCl<sub>3</sub>/BTEA-Cl/MeCN) for **1a** → **5a**, and method 4 (nucleoside/NH<sub>3</sub>/MeOH/Δ) for **3a** → **4**. Analogous reactions with equivalent molar proportions of other nucleosides gave the indicated products and quantities.

### **Example 1**

**Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-amino-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (**2a**).** Method 1. Et<sub>3</sub>N (1.25 mL, 910 mg, 9.0 mmol) was added to a stirred solution of ~~1a~~ **1a** (1.67 g, 4.8 mmol), TiPBS-Cl (2.73 g, 9.0 mmol), and DMAP (72 mg, 0.6 mmol) in dried CHCl<sub>3</sub> (70 mL) under N<sub>2</sub>. Stirring was continued for 24 h, and volatiles were evaporated. The orange residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) give **2a**<sup>32</sup> (2.67 g, 91%) as a slightly yellow foam with UV max 238, 291 nm, min 264 nm; <sup>1</sup>H NMR (500 MHz) δ 1.26–1.32 (m, 18H), 2.08 (s, 3H), 2.14 (s, 3H), 2.54 (ddd, *J* = 4.7, 9.0, 14.0 Hz, 1H), 2.91–2.99 (m, 2H), 4.22–4.37 (m, 3H), 4.43–4.47 (m, 2H), 4.97 (br s, 2H), 5.41–5.42 ("d", 1H), 6.26–6.29 (m, 1H), 7.21 (s, 2H), 7.84 (s, 1H); LRMS *m/z* 618 (MH<sup>+</sup> [C<sub>29</sub>H<sub>40</sub>N<sub>5</sub>O<sub>8</sub>S] = 618); HRMS *m/z* 640.2413 (MNa<sup>+</sup> [C<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>8</sub>SNa] = 640.2417).

### **Example 2**

**Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-*O*-(2,4,6-triisopropylbenzenesulfonyl) purine (**2b**).** Treatment of ~~1b~~ **1b** (950 mg, 2.0 mmol) by method 1 gave ~~2b~~ **2b** (1.27 g, 86%) as a white solid foam with UV max 289 nm, min 264 nm; <sup>1</sup>H NMR δ 1.29–1.32 (m, 18H), 2.76 (ddd, *J* = 2.1, 6.0, 14.3 Hz, 1H), 2.96 ("quint", *J* = 6.8 Hz, 1H), 3.15–3.25 (m, 1H), 4.34 ("quint", *J* = 6.8 Hz, 2H), 4.65–

4.74 (m, 2H), 4.85–4.90 (m, 1 H), 5.00 (br s, 2H), 5.84–5.86 ("d", 1H), 6.38–6.43 (m, 1H), 7.30 (s, 2H), 7.44–7.55 (m, 4H), 7.58–7.69 (m, 2H), 7.85 (s, 1H), 8.04 (d,  $J = 7.1$  Hz, 2H), 8.11 (d,  $J = 7.1$  Hz, 2H); LRMS  $m/z$  742 ( $MH^+$  [ $C_{39}H_{44}N_5O_8S$ ] = 742), 764 ( $MNa^+$  [ $C_{39}H_{43}N_5O_8SNa$ ] = 764); HRMS  $m/z$  764.2730 ( $MNa^+$  [ $C_{39}H_{43}N_5O_8SNa$ ] = 764.2730).

### 5 **Example 3**

**Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-6-*O*-(4-methylbenzenesulfonyl)purine (2'b).** Et<sub>3</sub>N (700  $\mu$ L, 506 mg, 5.0 mmol) was added to a stirred solution of **1b** (1.43 g, 3.0 mmol), TsCl (858 mg, 4.5 mmol), and DMAP (36 mg, 0.3 mmol) in dried CHCl<sub>3</sub> (45 mL) under N<sub>2</sub>. Stirring was continued for 15 h, and volatiles were evaporated. The slightly yellow residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give **2'b** (1.68 g, 89%) as a white solid foam with UV max 300 nm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  2.43 (s, 3H), 2.73 (ddd,  $J = 2.1, 8.4, 14.4$  Hz, 1H), 3.17–3.27 ("quint",  $J = 7.2$  Hz, 1H), 4.52–4.65 (m, 3H), 5.76–5.78 ("d", 1H), 6.37–6.41 (m, 1H), 6.95 (br s, 2H), 7.47–7.73 (m, 8H), 7.95 (d,  $J = 7.8$  Hz, 2H), 8.03–8.11 (m, 4H), 8.30 (s, 1H); LRMS  $m/z$  630 ( $MH^+$  [ $C_{31}H_{28}N_5O_8S$ ] = 630),  $m/z$  652 ( $MNa^+$  [ $C_{31}H_{27}N_5O_8SNa$ ] = 652); HRMS  $m/z$  652.1467 ( $MNa^+$  [ $C_{31}H_{27}N_5O_8SNa$ ] = 652.1478).

### **Example 4**

**Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy- $\beta$ -D-erythro-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3a).** Method 2. A solution of AcCl (200  $\mu$ L, 220 mg, 2.8 mmol) in dried CH<sub>2</sub>Cl<sub>2</sub> (12 mL) under N<sub>2</sub> was chilled in a NaCl/ice/H<sub>2</sub>O bath (–5 to 0 °C) for 15 min. BTEA-NO<sub>2</sub> (520 mg, 2.2 mmol) was dissolved in dried CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and this solution was immediately added dropwise to the cold, stirred solution of AcCl/CH<sub>2</sub>Cl<sub>2</sub>. A solution of **2a-2a** (288 mg, 0.5 mmol) in dried CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was then added dropwise to the cold solution, and stirring was continued for 5 min (TLC, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 95:5, showed complete conversion of **2a-2a** into a single product). The

reaction mixture was added dropwise at a rapid rate to a cold (ice/H<sub>2</sub>O bath), vigorously stirred mixture of saturated NaHCO<sub>3</sub>/H<sub>2</sub>O (100 mL)//CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The layers were separated, and the organic phase was washed with cold (0 °C) H<sub>2</sub>O (2 X 100 mL) and dried (MgSO<sub>4</sub>) for 1 h. Volatiles were evaporated, and the residue was chromatographed

5 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give **3a-3a** (267 mg, 89%) as a white solid foam with UV max 240, 266 nm, min 255 nm; <sup>1</sup>H NMR (500 MHz) δ 1.24–1.31 (m, 18H), 2.08 (s, 3H), 2.13 (s, 3H), 2.67 (ddd, *J* = 2.5, 7.0, 15.5 Hz, 1H), 2.76–2.81 (m, 1H), 2.90–2.96 ("quint", *J* = 7.0 Hz, 1H), 4.28–4.33 ("quint", *J* = 7.0 Hz, 2H), 4.35–4.39 (m, 3H), 5.38–5.39 ("d", 1H), 6.42–6.45 (m, 1H), 7.22 (s, 2H), 8.23 (s, 1H); LRMS *m/z* 637 (MH<sup>+</sup> [C<sub>29</sub>H<sub>38</sub>ClN<sub>4</sub>O<sub>8</sub>S] = 637); HRMS *m/z* 10 659.1902 (MNa<sup>+</sup> [C<sub>29</sub>H<sub>37</sub>ClN<sub>4</sub>O<sub>8</sub>SNa] = 659.1918).

### **Example 5**

**Preparation of 9-(3,5-Di-*O*-benzoyl-2-deoxy-β-*D*-erythro-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3b).** Treatment **2b-2b** (1.20 g, 1.6 mmol) by method 2 gave **3b-3b** (1.10 g, 90%) as a yellow solid foam with UV max 230, 266 15 nm, min 255 nm; <sup>1</sup>H NMR δ 1.22–1.34 (m, 18H), 2.92–3.00 (m, 3H), 4.30–4.34 (m, 2H), 4.68–4.77 (m, 3H), 5.80–5.82 ("d", 1H), 6.54–6.57 (m, 1H), 7.42–7.64 (m, 8H), 8.00 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.26 (s, 1H); HRMS *m/z* 783.2224 (MNa<sup>+</sup> [C<sub>39</sub>H<sub>41</sub>ClN<sub>4</sub>O<sub>8</sub>SNa] = 783.2231).

### **Example 6**

20 **Preparation of 9-(3,5-Di-*O*-benzoyl-2-deoxy-β-*D*-erythro-pentofuranosyl)-2-chloro-6-*O*-(4-methylbenzenesulfonyl)purine (3'b).** Treatment of **2'b-2'b** (1.45 g, 2.3 mmol) by method 2 gave **3'b-3'b** (1.30 g, 87%) as a slightly yellow foam with UV max 267 nm, min 255 nm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.45 (s, 3H), 2.86 (ddd, *J* = 3.4, 6.2, 14.0 Hz, 1H), 3.21–3.30 ("quint", *J* = 7.0 Hz, 1H), 4.55–4.67 (m, 3H), 5.82–5.84 (m, 1H), 6.56–6.61 (m,

1H), 7.42–7.72 (m, 8H), 7.88 (d,  $J = 7.8$  Hz, 2H), 8.04–8.07 (m, 4H), 8.88 (s, 1H); HRMS  $m/z$  671.0983 ( $MNa^+$  [ $C_{31}H_{25}ClN_4O_8SNa$ ] = 671.0979).

### **Example 7**

#### **Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy- $\beta$ -D-*erythro*-pentofuranosyl)-2-amino-**

5 **6-chloropurine (5a). Method 3.** A mixture of **1a** (540 mg, 1.54 mmol), BTEA-Cl (710 mg, 3.1 mmol), *N,N*-dimethylaniline (215  $\mu$ L, 206 mg, 1.7 mmol), and POCl<sub>3</sub> (720  $\mu$ L, 1.2 g, 7.7 mmol) in MeCN (6 mL) was stirred in a preheated oil bath (85 °C) for 10 min. Volatiles were flash evaporated immediately (in vacuo), and the yellow foam was dissolved (CHCl<sub>3</sub>, 15 mL) and stirred vigorously with crushed ice for 15 min. The layers were separated, and  
10 the aqueous phase was extracted (CHCl<sub>3</sub>, 3 X 5 mL). Crushed ice was frequently added to the combined organic phase, which was washed [(ice-H<sub>2</sub>O (3 X 5 mL), 5% NaHCO<sub>3</sub>/H<sub>2</sub>O (to pH ~7)] and dried (MgSO<sub>4</sub>). Volatiles were evaporated, and the residue was chromatographed (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give **5a**<sup>36,39-38</sup> (517 mg, 90%) as a white solid foam with UV max 248, 310 nm, min 268 nm; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  2.02 (s, 3H), 2.08 (s, 3H), 2.49–2.52 (m, 1H), 3.04–3.06 (m, 1H), 4.20–4.29 (m, 3H), 5.32–5.34 ("d", 1H), 6.23–6.26 (m, 1H); 7.03 (br s, 2H), 8.35 (s, 1H); <sup>1</sup>H NMR  $\delta$  2.03 (s, 3H), 2.08 (s, 3H), 2.51 (ddd,  $J$  = 2.7, 5.9, 14.2 Hz, 1H), 2.85–2.94 ("quint",  $J = 7.1$  Hz, 1H), 4.28–4.42 (m, 3H), 5.35–5.37 (m, 1H), 6.21–6.26 (m, 1H), 7.89 (s, 1H); HRMS (EI)  $m/z$  369.0844 ( $M^+$  [ $C_{14}H_{16}ClN_5O_5$ ] = 369.0840).

### 20 **Example 8**

#### **Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy- $\beta$ -D-*erythro*-**

**pentofuranosyl)-6-chloropurine (5b).** Treatment of **1b** (2.38 g, 5 mmol) by method 3 gave **5b** (2.10 g, 85%) as a slightly yellow solid foam with UV max 310 nm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  2.69–2.78 ("ddd", 1H), 3.20–3.24 ("quint",  $J = 7.2$  Hz, 1H), 4.56–4.67 (m, 3H), 5.77–5.79 ("d", 1H), 6.39–6.44 (m, 1H), 7.02 (br s, 2H), 7.48–7.71 (m, 6H), 7.96 (d,  $J = 8.4$  Hz, 2H),

8.06 (d,  $J = 8.7$  Hz, 2H), 8.37 (s, 1H); LRMS  $m/z$  494 ( $MH^+$  [ $C_{24}H_{21}ClN_5O_5$ ] = 494); HRMS  $m/z$  516.1042 ( $MNa^+$  [ $C_{24}H_{20}ClN_5O_5Na$ ] = 516.1051).

### **Example 9**

#### **Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy- $\beta$ -D-*erythro*-pentofuranosyl)-2,6-**

5 **dichloropurine (6a).** Treatment of **5a** (265 mg, 0.7 mmol) by method 2 gave **6a**<sup>4039</sup> (266 mg, 95%) as a white solid foam with UV max 274 nm, min 232 nm;  $^1H$  NMR (500 MHz)  $\delta$  2.12 (s, 3H), 2.15 (s, 3H), 2.73 (dddd,  $J = 2.4, 5.9, 14.2$  Hz, 1H), 2.83–2.86 (m, 1H), 4.38–4.39 (m, 3H), 5.41–5.42 ("d", 1H), 6.45–6.50 (m, 1H), 8.33 (s, 1H); HRMS  $m/z$  411.0230 ( $MNa^+$  [ $C_{14}H_{14}Cl_2N_4O_5Na$ ] = 411.0239).

### 10 **Example 10**

#### **Preparation of 9-(3,5-Di-*O*-benzoyl-2-deoxy- $\beta$ -D-*erythro*-pentofuranosyl)-2,6-**

**dichloropurine (6b).** Treatment of **5b** (407 mg, 0.8 mmol) by method 2 gave **6b** (386 mg, 91%) as a slightly yellow solid foam with UV max 274 nm, min 257 nm;  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  2.87 (ddd,  $J = 3.5, 8.0, 17.5$  Hz, 1H), 3.25–3.31 (m, 1H), 4.57–4.71 (m, 15 3H), 5.83–5.85 ("d", 1H), 6.59–6.62 (m, 1H), 7.46–7.72 (m, 6H), 7.91 (d,  $J = 7.5$  Hz, 2H), 8.09 (d,  $J = 7.5$  Hz, 2H), 8.96 (s, 1H); HRMS  $m/z$  535.0562 ( $MNa^+$  [ $C_{24}H_{18}Cl_2N_4O_5Na$ ] = 535.0552).

### **Example 11**

#### **Preparation of 2-Chloro-2'-deoxyadenosine (Cladribine, 4). Method 4.**

20  $NH_3/MeOH$  (12 mL, saturated at 0 °C) was added to a solution of **3a** (159 mg, 0.25 mmol) in  $CH_2Cl_2$  (8 mL) in a pressure tube. The tube was sealed and immediately immersed in an oil bath preheated to 80 °C. Heating (80 °C) was continued for 7 h, and volatiles were evaporated. The residue was dissolved ( $H_2O$ , 2 mL), and the solution was applied to a column of Dowex 1 X 2 ( $OH^-$ , 20 mL), the flask was rinsed ( $H_2O$ , 5 mL) and applied to the  
25 column. The column was washed ( $H_2O$ ) until the pH of the eluate was neutral, and then



MeOH/H<sub>2</sub>O (1:1) was applied. UV-absorbing fractions were pooled, and volatiles were evaporated. EtOH (3 X 10 mL) was added and evaporated, and the residue was dried (in vacuo) to give **4** (58 mg, 81%). The white powder was recrystallized from MeOH to give **4** (2 crops, 84% recovery) with mp >300 °C (crystals slowly became brown at ~220 °C), or  
 5 from H<sub>2</sub>O (2 crops, 72% recovery) with mp >300 °C (Lit. mp softening at 210–215 °C,<sup>16</sup> then dec.; >300 °C;<sup>18,21</sup> 232 °C); UV, <sup>1</sup>H NMR, and MS data were in agreement with published values.<sup>21,22</sup> Anal. Calcd for C<sub>10</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub>: C, 42.04; H, 4.23; N, 24.51. Found: C, 41.85; H, 4.40; N, 24.46.

Treatment of **3b** (83%), **3'b** (43%), **6a** (87%), or **6b** (94%) by method 4 gave **4** as  
 10 white, TLC homogeneous powders with identical spectral data.

### **Example 12**

#### **Preparation of 9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloropurine (**8**).**

**Method A.** TMS-Cl (1.14 mL, 978 mg, 9.0 mmol) was added dropwise to a stirred solution of **7** (428 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) under N<sub>2</sub>. BTEA-NO<sub>2</sub> (714 mg, 3.0  
 15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise (1 drop/2 sec) and the solution was stirred at ambient temperature for 30 min (TLC). The solution was diluted (CH<sub>2</sub>Cl<sub>2</sub>, 200 mL) and washed (5% NaHCO<sub>3</sub>/H<sub>2</sub>O, 5 x 100 mL). The combined aqueous phase was extracted (CH<sub>2</sub>Cl<sub>2</sub>, 2 x 100 mL), and the combined organic phase was dried (MgSO<sub>4</sub>) and filtered. Volatiles were evaporated, Et<sub>2</sub>O was added to and evaporated (3 x 25 mL) from the yellow  
 20 oil, and the residue was recrystallized (EtOH) to give **8** (373 mg, 83%) as pale-yellow crystals with mp, UV, <sup>1</sup>H NMR, and MS data as reported.<sup>27</sup>

**Method B.** TMS-Cl (444, uL, 280 mg, 3.50 mmol) was added to dropwise to a stirred mixture of **7** (428 mg, 1.0 mmol) and powdered NaNO<sub>2</sub> (345 mg, 5.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) under N<sub>2</sub>. BTEA-NO<sub>2</sub> (357 mg, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added dropwise (1  
 25 drop/sec) and the solution was stirred at ambient temperature for 1 h (TLC). The mixture

was cooled for 15 min and added dropwise to a cold, vigorously stirred mixture of saturated  $\text{NaHCO}_3/\text{H}_2\text{O}$  (200 mL)/ $\text{CH}_2\text{Cl}_2$  (200 mL). The aqueous layer was extracted ( $\text{CH}_2\text{Cl}_2$  100 mL), and the combined organic phase was washed ( $\text{H}_2\text{O}$ , 100 mL) and dried  $\text{MgSO}_4$ . Volatiles were evaporated, and the yellow oil was recrystallized ( $\text{BuOH}$ ) to give **8** (384 mg, 85%) as pale-yellow crystals.

**Method C.** A solution of  $\text{AcCl}/\text{CH}_2\text{Cl}_2$  (1 M, 2.5 mL, 2.5 mmol) was added to dried  $\text{CH}_2\text{Cl}_2$  (10 mL) under  $\text{N}_2$ , and the solution was cooled for 15 min.  $\text{BTEA-NO}_2$  (535.5 mg, 2.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was then added dropwise (1 drop/2 sec) to the cold, stirred solution of  $\text{AcCl}/\text{CH}_2\text{Cl}_2$ . A cold solution of **7** (214 mg., 0.5 mmol) in dried  $\text{CH}_2\text{Cl}_2$  (5 mL) was then added dropwise to the cooled, stirred  $\text{AcCl}/\text{BTEA-NO}_2/\text{CH}_2\text{Cl}_2$  solution (TLC, ~~hexanes~~ hexanes/EtOAc, 3:7). Immediate workup and recrystallization (as in method B) gave **8** (187 mg, 84%) as pale-yellow crystals.

**Endnotes:**


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<sup>1</sup> (a) Carson, D. A.; Wasson, D. B.; Kaye, J.; Ullman, B.; Martin, D. W., Jr.; Robins, R. K.; Montgomery, J. A. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 6865–6869. (b) Carson, D. A.; Wasson, D. B.; Taetle, R.; Yu, A. *Blood* **1983**, *62*, 737–743.

<sup>2</sup> Piro, L.D., Carrera, C.J.; Carson, D. A.; Beutler, E. N. *Engl. J. Med.* **1990**, *322*, 1117–1121.

<sup>3</sup> Jehn, U.; Bartl, R.; Dietzfelbinger, H.; Vehling-Kaiser, U.; Wolf-Hornung, B.; Hill, W.; Heinemann, V. *Ann. Hematol.* **1999**, *78*, 139–144.

<sup>4</sup> Piro, L. D.; Carrera, C. J.; Beutler, E., Carson, D. A. *Blood* **1988**, *72*, 1069–1073.

<sup>5</sup> Mitterbauer, M.; Hilgenfeld, E.; Wilfing, A.; Jäger, U.; Knauf, W. U. *Leukemia* **1997**, *11*, Suppl. 2, S35–S37.

<sup>6</sup> Kong, L. R.; Huang, C.-F.; Hakimian, D.; Variakojis, D.; Klein, L.; Kuzel, T. M.; Gordon, L. I.; Zanzig, C.; Wollins, E.; Tallman, M. S. *Cancer* **1998**, *82*, 957–964.

<sup>7</sup> Hellmann, A.; Lewandowski, K.; Zaucha, J. M.; Bieniaszewska, M.; Halaburda, K.; Robak, T. *Eur. J. Haematol.* **1999**, *63*, 35–41.

<sup>8</sup> Beutler, E.; Sipe, J.; Romine, J.; McMillan, R.; Zyroff, J.; Koziol, J. *Semin. Hematol.* **1996**, *33*, Suppl. 1, 45–52.

<sup>9</sup> Davis, J. C., Jr.; Austin, H., III; Boumpas, D.; Fleisher, T. A.; Yarboro, C.; Larson, A.; Balow, J.; Klippel, J. H.; Scott, D. *Arthritis Rheum.* **1998**, *41*, 335–343.

<sup>10</sup> (a) Wang, L.; Karlsson, A.; Arnér, E. S. J.; Eriksson, S. *J. Biol. Chem.* **1993**, *268*, 22847–22852. (b) Sjöberg, A. H.; Wang, L.; Eriksson, S. *Mol. Pharmacol.* **1998**, *53*, 270–273.

<sup>11</sup> Genini, D.; Adachi, S.; Chao, Q.; Rose, D. W.; Carrera, C. J.; Cottam, H. B.; Carson, D. A.; Leoni, L. M. *Blood*, **2000**, *96*, 3537–3543.

- 
- <sup>12</sup> Marzo, I.; Pérez-Galán, P.; Giraldo, P.; Rubio-Félix, D.; Anel, A.; Naval, J. *Biochem. J.* **2001**, *359*, 537–546.
- <sup>13</sup> Venner, H. *Chem. Ber.* **1960**, *93*, 140–149.
- <sup>14</sup> Ikehara, M.; Tada, H. *J. Am. Chem. Soc.* **1965**, *87*, 606–610.
- <sup>15</sup> Robins, M. J.; Robins, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 4934–4940.
- <sup>16</sup> Christensen, L. F.; Broom, A. D.; Robins, M. J.; Bloch, A. *J. Med. Chem.* **1972**, *15*, 735–739.
- <sup>17</sup> Seela, F.; Kehne, A. *Liebigs Ann. Chem.* **1983**, 876–884.
- <sup>18</sup> Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379–6382.
- <sup>19</sup> Robins, R. K.; Revankar, G. R. U.S. Patent 4,760,137, 1988; also see *Chem. Abstr.* **1986**, *105*, 60911u.
- <sup>20</sup> Hildebrand, C.; Wright, G. E. *J. Org. Chem.* **1992**, *57*, 1808–1813.
- <sup>21</sup> Worthington, V. L.; Fraser, W.; Schwalbe, C. H. *Carbohydr. Res.* **1995**, *275*, 275–284.
- <sup>22</sup> Votruba, I.; Holy, A.; Dvoráková, H.; Gunter, J.; Hocková, D.; Hrebabecky, H.; Cihlár, T.; Masojídková, M. *Collect. Czech. Chem. Commun.* **1994**, *59*, 2303–2330.
- <sup>23</sup> Barai, V. N.; Zinchenko, A. I.; Eroshevskaya, L. A.; Zhernosek, E. V.; De Clercq, E.; Mikhailopulo, I. A. *Helv. Chim. Acta* **2002**, *85*, 1893–1900.
- <sup>24</sup> Robins, M. J.; Zou, R.; Hansske, F.; Wnuk, S. F. *Can. J. Chem.* **1997**, *75*, 762–767.
- <sup>25</sup> Barai, V. N.; Zinchenko, A. I.; Eroshevskaya, L. A.; Kalinichenko, E. N.; Kulak, T. I.; Mikhailopulo, I. A. *Helv. Chim. Acta* **2002**, *85*, 1901–1908.
- <sup>26</sup> (a) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601–2607. (b) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2608–2611.

- 
- <sup>27</sup> Francom, P., Janeba, Z.; ~~Shibya~~ Shibuya, S.; Robins, M.J. *J. Org. Chem.*, **2002**, *67*, 6788-6796.
- <sup>28</sup> (a) Bridson, P. K.; Markiewicz, W.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1977**, 447-448. (b) Bridson, P. K.; Markiewicz, W. T.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1977**, 791-792.
- <sup>29</sup> Daskalov, H. P.; Sekine, M.; Hata, T. *Tetrahedron Lett.* **1980**, *21*, 3899-3902.
- <sup>30</sup> Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, *23*, 2253-2256.
- <sup>31</sup> Matsuda, A.; Shinozaki, M.; Suzuki, M.; Watanabe, K.; Miyasaka, T. *Synthesis* **1986**, 385-386
- <sup>32</sup> McGuinness, B. F.; Nakanishi, K.; Lipman, R.; Tomasz, M. *Tetrahedron Lett.* **1988**, *29*, 4673-4676.
- <sup>33</sup> Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945-948.
- <sup>34</sup> Mehta, J. R.; Ludlum, D. B. *Biochim. Biophys. Acta* **1978**, *521*, 770-778.
- <sup>35</sup> Nandan, E.; Camaioni, E.; Jang, S.-Y.; Kim, Y.-C.; Cristalli, G.; Herdewijn, P.; Secrist, J. A., III; Tiwari, K. N.; Mohanram, A.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 1625-1638.
- <sup>36</sup> Kamaike, K.; Kinoshita, K.; Niwa, K.; Hirose, K.; Suzuki, K.; Ishido, Y. *Nucleosides, Nucleotides, Nucleic Acids* **2001**, *20*, 59-75.
- <sup>37</sup> Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670-672.
- <sup>38</sup> Montgomery, J. A.; Hewson, K. *J. Med. Chem.* **1969**, *12*, 498-504.
- <sup>39</sup> ~~Montgomery, J. A.; Hewson, K. *J. Med. Chem.* **1969**, *12*, 498-504.~~
- <sup>4039</sup> Gerster, J.F.; Jones, J.W.; Robins, R.K., *J. Org. Chem.* **1963**, *23*, 945-948.

**ABSTRACT OF THE INVENTION**

The present invention is a method for preparing 2-halo-6-aminopurines, and more specifically for preparing the clinical agent cladribine (2-chloro-2'-deoxyadenosine, CldAdo, 4), a drug of choice against hairy-cell leukemia and other neoplasms, from 2-amino-6-oxopurines, which are readily obtained from the naturally occurring compound 2'-deoxyguanosine. According to the methods of the present invention, the 6-oxo group of a protected 2'-deoxyguanosine (1) is converted to a 6-(substituted oxy) leaving group, or alternatively to a 6-chloro leaving group, the 2-amino group is replaced with a 2-chloro group, the 6-(substituted oxy) leaving group, or alternatively the 6-chloro leaving group, is replaced with a 6-amino group or, alternatively, a 2,6-dichloro substituted compound is selectively replaced with a 6-amino group, and the protecting groups are removed.